American Journal of Medical Genetics 64:373–375 (1996)

FRAXA Premutation Associated With Premature Ovarian Failure

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A family is described in which six females in three generations experienced premature ovarian failure (POF). In three of them a FRAXA premutation was documented and the carrier status of a fourth female could be inferred, because her son had the fragile X syndrome. These findings provide further evidence for a nonrandom association between POF and the FRAXA premutation.

KEY WORDS: premature ovarian failure, premature menopause, FRAXA premutation, FRAXA heterozygotes

INTRODUCTION

Premature ovarian failure (POF) is the cessation of ovarian functioning before the age of 40 years. It has been described both in patients with abnormalities of the X chromosome and in association with a normal karyotype. Familial cases clearly show a pattern of dominant inheritance, with expression restricted to females [Mattison et al., 1984]. A family in which women in at least three generations had POF and an interstitial deletion of Xq with breakpoints at Xq21.3-q22 and Xq26-q27 suggests that the disruption of gene(s) on Xq causes POF [Krauss et al., 1987]. Previously, Fitch et al. [1982] had described two sisters with POF and a Xq deletion probably encompassing Xq26-q28.

The most common fra(X) syndrome mutation is an amplification of a CGG repeat in the first exon of the FMR1 gene at Xq27 [Oberlé et al., 1991; Verkerk et al., 1991; Kremer et al., 1991]. Whereas the number of repeats exceeds 200 in affected individuals (full mutation), normal carriers have 50–200 CGG repeats which characterize the premutation. The fully mutated allele is associated with the hypermethylation of the adjacent CpG island [Oberlé et al., 1991; Malmgren et al., 1992] and is not transcribed [Pieretti et al., 1991].

Received for publication September 27, 1995.

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A possible association of the FRAXA mutation and POF was first investigated by Cronister et al. [1991] who found eight women with POF among 61 normal fra(X) heterozygotes. In a multicenter study of obstetrical and gynecological complications in fra(X) carriers, that included 92 premutated females, Schwartz et al. [1994] found that the carriers had POF (25%) more frequently than noncarriers (6%). More recently, Murray et al. [1995] identified two FRAXA premutation carriers among nine women with familial POF.

Here we describe a three generation family in which POF segregates in association with the FRAXA premutation.

MATERIALS AND METHODS

DNA Analysis

DNA extracted from whole blood was doubly digested with *EcoRI/EagI* and probed with *StB12.3,* as previously described [Mingroni-Netto et al., 1994].

CLINICAL REPORTS

The family (Fig. 1) was ascertained by us through III-1, because of POF. In addition to other cases of POF, family history included a boy diagnosed elsewhere as having fra(X) syndrome. This prompted us to investigate a possible association of POF with the FRAXA mutation.

Six females with POF were identified in the family:

1. I-2 is the carrier of a FRAXA premutation (Δ = 100 bp) and had menopause at about 40 years of age.
2. II-2 ceased menstruation at age 24. She refused to be tested for FRAXA mutation.
3. II-3 had premature menopause when she was 35 years old. Her fra(X) carrier status can be inferred from the presence of the mutation in her affected son.
4. II-6. She had menses just for a few months after menarche at 14 yrs of age. She carries the FRAXA premutation (Δ = 200 bp).
5. II-7 is said to have experienced premature menopause.
6. III-1 presented a clinical picture of POF at 16 years of age. She carries a FRAXA premutation (Δ = 100 bp). The premutation was inherited from her normal father (Δ = 200 bp).

In the offspring of I-2, there was only one female who did not have POF. She is not a carrier of a FRAXA premutation.

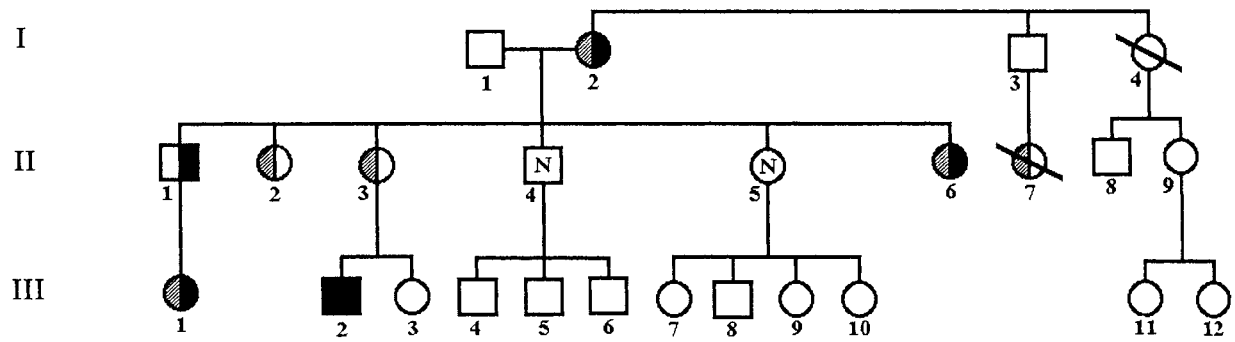

Fig. 1. Segregation of premature ovarian failure (POF) in association with FRAXA premutation through three generations, including transmission by a male (II-1). ■ = Fra(X) syndrome; ◍ = POF/FRAXA premutation; ◐ = POF/FRAXA not investigated; ◨ = normal phenotype/FRAXA premutation; [N] Ⓝ = normal phenotype/no FRAXA mutation; □○ = normal phenotype/FRAXA not investigated.

DISCUSSION

There is now a good amount of evidence in the literature pointing to a causal association of POF and the expansion of the CGG repeats of the FMR1 gene in the premutation range. The findings of Cronister et al. [1991], suggesting an increased risk of premature menopause among fra(X) carriers, were confirmed by a multicenter study [Schwartz et al., 1994] that showed that premutation carriers experienced cessation of menses prior to age 40 years at a significantly higher rate than controls. The authors suggested that the genetic defect in FMR1 could prevent normal numbers of oocytes from being produced.

More recently, Turner et al. [1994] commenting on their data that showed an increased probability of FRAXA carriers to give birth to dizygous twinning, concluded that these heterozygotes might be specially prone to POF, since menopause might occur earlier in multiple ovulators.

But further evidence for an influence of the FRAXA premutation on ovarian function was provided by Murray et al. [1995], when they found 2/9 women with familial POF to have FRAXA premutations. The premutation was not present in the 37 females with sporadic POF. The family here described adds further support to the hypothesis of the nonrandom nature of the association. The premutation was documented in the three patients with POF that were investigated, and a fourth female, also with POF, certainly was a FRAXA carrier, because she had a son affected by fra(X) syndrome.

Since it is the premutation and not the full mutation that appears to influence ovarian function, the effect should not be the result of a loss of function of the FMR1 gene. Otherwise, as Murray et al. [1995] suggested, one of the FMR1 isoforms could be inappropriately expressed in the fetal ovary of premutated females. Another possibility is that the premutation affects a nearby gene (or genes) for ovarian function, inducing abnormal methylation. The existence of such gene(s) in the vicinity of the FMR1 locus is indicated by the Xq distal deletions described in females with POF [Fitch et al., 1982; Krauss et al., 1987].

The fact that the association clusters in families is suggestive of a peculiarity of some premutations themselves and/or of the gene(s) they influence.

ACKNOWLEDGMENTS

This work was partly supported by FAPESP and CNPq.

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